REMARKS

After entry of the present amendment, Claims 1-11 and 61 will stand cancelled, Claims 12-18, 28-36, 45-55, 59-60, and 62-65 will stand currently amended, Claims 19-20, 22, 26, 38-39, 41, and 56-57, and 66-67 will stand withdrawn but currently amended, and Claims 21, 23-25, 27, 37, 30, 42-44, 58, and 66-67 will stand withdrawn.

The claims were amended to change the term "drug delivery device" to "drug delivery composition," as suggested by the Examiner. Claims 65 and 69 were amended to change the term "treating ulcerative colitis or Crohn's disease" to "treating the symptoms of ulcerative colitis or Crohn's disease," as suggested by the Examiner.

Claims 19 and 62 were amended to correct the dependency.

New Claims 70-73 are dependent claims, dependent on each of the currently pending independent claims, and specifying that the isolated active agent which inactivates an antibiotic is a beta-lactamase. Support for a beta-lactamase as the active agent is found throughout the application.

No new matter is added by the amendment.

Attached along with this Amendment is a Declaration under 37 C.F.R. 1.132 of Antoine Andremont, M.D., Ph.D. The Declaration is being submitted in support of the enablement of the claims, the novelty of the claims due to the failure of the art cited in the novelty rejection to include various elements of the claims, and the lack of obviousness of the claimed invention over the cited references.

Rejections under 35 U.S.C. 112, First Paragraph

Claim 65 was rejected under 35 U.S.C. 112, first paragraph, as non-enabled. The purported basis for the rejection is that the claim is directed to the treatment of ulcerative colitis or Crohn's disease, whereas the Examiner believes that it is only possible to treat the symptoms of ulcerative colitis or Crohn's disease.

While Applicants respectfully disagree, they have limited the claims to treating the symptoms of ulcerative colitis or Crohn's disease. The Examiner is respectfully requested to withdraw the rejection in light of the amendment to the claim.

Withdrawn claim 69 is a method claim with the same "treating ulcerative colitis or Crohn's disease" language, so was amended in accordance with the amendment to Claim 65, in the event of rejoinder.

Rejections under 35 U.S.C. 112, Second Paragraph

Rejections Related to the Term "Drug Delivery Device"

Claims 12-18, 28-36, 45-55, 59, 60, and 62-65 were rejected under 35 U.S.C. 112, second paragraph, as purportedly indefinite. The purported basis for the rejection involves the terminology "drug delivery device," in that the Examiner indicated that it is unclear how a device could comprise a device, and that the term "device" is in a different statutory classification than a composition of matter, such as an active agent or chemical composition.

It is well-settled law that Applicants are entitled to be their own lexicographer, and the meaning of the claim terms as previously pending was clear. That is, it was clear that the claims

were directed to a composition that included an active agent and a composition for delivering the active agent to the colon. Because the composition delivers the active agent to the colon, it was termed a "drug delivery device."

To facilitate prosecution, Applicants have amended the claims to be directed to "drug delivery compositions." It is clear that the drug delivery compositions include an active agent and a composition for delivering the active agent to the colon, wherein the active agent is incorporated into the composition. Applicants respectfully traverse the rejections if applied to the amended claims.

Rejections Related to the Term "Isolated"

Claims 12, 28, 35, 45, and 59 were rejected under 35 U.S.C. 112, second paragraph, as indefinite for use of the term "isolated." The purported basis of the rejection is that the claim is indefinite, because the requisite degree of isolation is not provided. That is, there is purportedly no reference point to distinguish over the compositions made of record (i.e., which delivered whole bacteria rather than an isolated enzyme). Applicants respectfully traverse.

First and foremost, a U.S. patent is deemed to be enabled, and over twenty thousand U.S. patents include claims with the term "isolated" and have specifications referring to enzymatic activity. A reasonable number of these include claims related to isolated enzymes. Similarly, by substituting the terms "DNA," "peptide," or "protein," the number of issued patents is similarly around 20,000 for each of these terms. While Applicant has not done an exhaustive search of all of these patents, one thing is clear. Numerous claims in issued patents, presumed to be enabled, include the term "isolated" without describing, within the claim, the "requisite degree of

isolation." If those claims in these issued patents which claim isolated biological material were examined using the criteria the Examiner has proposed, numerous issued patents would be invalid as non-enabled.

Notwithstanding the above, the specification clearly points out that the drug delivery compositions are intended to deliver an isolated enzyme, rather than a bacteria that produces an enzyme.

In the specification as published, Applicants point out limitations associated with the prior art colonic delivery of whole bacteria that produce β-lactamase enzymes, namely, that they may transfer the drug resistance to the commensal flora (See paragraph [0050]). Thus, it is clear that the claimed compositions are intended for delivering isolated enzymes, rather than whole bacteria.

Each of the working examples that discusses delivering a β-lactamase refers to enzymatic activity (measured in terms of UI/bead). If live bacteria were administered, there would be no mention of enzymatic activity in terms of UI/bead, because the bacteria would simply keep on producing the enzyme (i.e., unlimited activity. Thus, there would have been, in theory, infinite activity, so long as the bacteria remained alive.

The specification also refers to specific isolated enzymes that can be incorporated into the drug delivery compositions. For example, paragraph [0057] specifically lists the erythromycin esterase described by Andremont A. et al.((1985), Infect. Immun. 49 (3), 751) and the enzyme capable of inactivating quinolones described by Chen Y et al.((1997) Journal of Industrial Microbiology and Biotechnology 19, 378).

The specification further teaches preparing pectin beads encapsulating an isolated beta-lactamase. For example, paragraph [0085] states that "[f]or preparation of loaded beads the active ingredient (β-lactamases, penicillinases of type A extracted from Bacillus cereus by Sigma) was mixed in with the solution of pectin in a ratio of 3% (Vpa/Vpectin).

The specification further teaches a process for isolating enzymes from whole bacteria. That is, Example 6 shows a process for producing an isolated enzyme. For example, paragraph [0129] teaches that the enzyme erythromycin esterase is an intracellular enzyme, and its solubilization required the cells to be broken (i.e., the bacteria had to be totally destroyed to obtain the isolated enzyme). This operation was carried out by ultrasonic extraction of centrifuging caps recovered in the potassium phosphate buffer 5 mM, pH 7.5.

The fact that the working examples (See Examples 1-6) focused on the enzymatic activity before and after delivery shows that the enzymes were not only isolated, they were capable of being administered to the colon and still retain enzymatic activity.

Thus, the specification clearly teaches:

a) how the prior art delivery of whole bacteria producing β-lactamases was unsuccessful (Paragraph 0050),

b) Examples of isolated enzymes in the literature that can be used,

c) How to prepare isolated enzymes, and how to incorporate the isolated enzymes into pectin beads,

d) How to measure enzyme activity both before and after administration of the drug delivery compositions to ensure that the enzyme activity was preserved throughout transit, and

e) that the compositions described in the specification were capable of achieving the desired drug delivery.

Based on the foregoing, it is clear that the specification provides an adequate description of "isolated" active agents. The term "isolated" is supported by the specification and overcomes both the previously-raised rejection under 35 U.S.C. 101 and the previously-raised rejection under 35 U.S.C. 102 (b).

Applicants respectfully submit that the "degree of isolation" referred to by the Examiner is not the relevant consideration, since those of skill in the art know how to isolate enzymes from bacteria. A simple Google search for the terms "isolation of enzymes from bacteria" produced more than two million hits. Isolated β-lactamase enzymes were not only commercially available at the time the application was filed, representative commercially-available enzymes were described in the specification. Rather, Applicants submit that the need for isolating the enzyme, and delivering the isolated enzyme to the colon (rather than a bacteria that might produce the enzyme), while maintaining enzymatic activity, are the relevant considerations.

Again, the specification discusses the need to deliver the isolated enzyme, and to avoid delivering a bacteria, in terms of the spread of bacterial resistance to antibiotics from the delivered bacteria to the native bacteria (i.e., "engendering a risk of dissemination of these genes within the colonic ecosystem and in the environment" (paragraph [0050] of the published application).

In view of the foregoing, the Examiner is respectfully requested to withdraw the enablement rejection. If the Examiner is inclined to maintain this rejection, he is encouraged to

first consider the Declaration under 37 C.F.R. 1.132 of Antoine Andremont, M.D., Ph.D., submitted herein.

If, even after reviewing the arguments and Declaration presented herein, the Examiner is still inclined to maintain this rejection, he is encouraged to suggest alternative claim language to indicate that the active agent, rather than a bacteria which might produce the active agent, but which might also disseminate genes related to antibiotic resistance throughout the commensal flora, is administered using the claimed drug delivery compositions.

Rejections under 35 U.S.C. 102 (b)

Claims 12-14, 28-31, 36, 59-62, and 65 were rejected under 35 U.S.C. 102 (b) as anticipated by U.S. Patent No. 6,500,423 to Olshenitsky, as evidenced by Arthur, Annales de l'Institut Pasteur, Microbiologie 137(1.1) Jan/Feb 1986, pages 125-134 and Ounissi and Courvalin, P. Gene 1985, 35(3), pages 271-278. This rejection is respectfully traversed, on the basis that the cited art does not teach administering isolated enzymes, and on the basis that the cited art does not support a novelty rejection, as the teachings of the art are misstated in the Office Action.

The Claimed Subject Matter

The claims are directed to drug delivery compositions which include an isolated active agent capable of inactivating antibiotics. As discussed in great detail above, the use of isolated active agents, rather than whole bacteria, is essential to the invention (again, see Paragraph [0050]). Further, the commercial availability of isolated active agents, the production of same by

destroying bacterial cells, and the incorporation of isolated active agents into pectin beads (i.e., rather than whole bacteria), is taught throughout the specification.

Olshenitski

Olshenitski purportedly teaches a composition comprising an active agent (a probiotic) and a drug delivery device. The active agent is a specific E. Coli - E. coli ATCC Deposit No. 202226.

Arthur, Annales de l'Institut Pasteur, Microbiologie 137(1.1) Jan/Feb 1986, pages 125-134 and Ounissi and Courvalin, P. Gene 1985, 35(3), pages 271-278.

These secondary references were cited for the proposition that probiotics (bacteria) inherently produce agents that might contain/produce erythromycin esterase. This proposition is untrue. Arthur discloses that the authors (including Antoine Andremont, M.D., Ph.D., one of the inventors of the instant patent claims) constructed a probe specific for the gene ereA of plasmid plP1100, which confers resistance to erythromycin in E. coli strains that include this gene. While there are certain E. coli strains that include this gene, there is no evidence that the gene is inherently present in all, or even most, E. coli, let alone the specific E. coli (ATCC Deposit No. 202226) in the cited Olshenitski reference.

Analysis

Erroneous Application of the Law of Inherency

The Office Action asserts that E. coli inherently produce erythromycin esterase. While it is true that some strains of E. coli do produce erythromycin esterase, it is absolutely not the case that all E. coli produce erythromycin esterase. If such were true, that would indicate that the entire human population had commensal flora which are immune to erythromycin antibiotics.

Respectfully, the inherency analysis in the Office Action is flawed. While a claim is anticipated, and thus invalid, if a single reference, inherently discloses every limitation of the claim at issue (*MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999) (quoting *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997)), inherency must be a "deliberate or necessary consequence" of the reference's disclosure. An inherent disclosure must flow naturally from the teachings of the prior art reference. *MEHL*, 192 F.3d at 1365 (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)).

The Court of Appeals for the Federal Circuit ("CAFC") analyzes inherent disclosures on the basis of requiring an inherency to be "necessarily present" and not merely sometimes, occasionally, or possibly present. At the patent prosecution stage, the United States Patent and Trademark Office similarly requires an examiner to supply an applicant either with a rationale for the inherent disclosure or evidence demonstrating the presence of the inherency. United States Patent and Trademark Office, Manual of Patent Examining Procedure § 2112 (8th ed. rev. 1, Feb. 2003) [hereinafter MPEP].

The Office Action provides no evidence that all E. coli inherently produce erythromycin esterase, that the majority produce this enzyme, or even that the specific E. coli in Olshenitski produces this enzyme. Indeed, no such evidence can be provided, as this is a technically flawed conclusion. At best, the cited references teach that some E. coli produce the gene ereA, which

confers resistance to erythromycin. In support of this argument, the Examiner is encouraged to review the attached Declaration under 37 C.F.R. of Antoine Andremont, M.D., Ph.D.

Accordingly, even if the Examiner was to totally ignore the fact that the claims relate to the administration of isolated active agents (i.e., isolated enzymes such as erythromycin esterase and β-lactamase rather than whole bacteria), it does not follow that Olshenitski inherently teaches each element of the claims. The rejection should be withdrawn on this basis alone.

Should the Examiner seek to provide an obviousness rejection, by modifying Olshenitski such that the probiotic actually include the ereA gene, he should consider that there would be no motivation to do so. Olshenitski's purpose for using a probiotic is to either avoid using an antibiotic altogether, or, where the antibiotic destroys both good and bad bacteria, the probiotic replaces only the good bacteria. There would be no motivation to modify the probiotic such that it would destroy any erythromycin that was administered and that arrived at the colon. Such a modification would inure to the benefit of bad bacteria present in the colon, as the erythromycin antibiotic would be inactivated before it could destroy them. Further, if a naturally-occurring bacterial strain worked (i.e., treated the bacterial overgrowth of bad bacteria in the colon), there would be no reason to introduce a genetically modified strain. Still further, the probiotic was designed to increase in population density in the patient's colon. Filling the patient's colon with an antimicrobial-resistant bacteria, which can transfer the resistance to other bacteria, is exactly the opposite of the goal of the claimed invention – avoiding the development of antimicrobial-resistant bacteria in the colon. Accordingly, there would be no logical basis to combine the references as the Examiner has suggested, either for a faulty inherency analysis, or in an obviousness rejection.

Administration of Isolated Enzymes Offers Advantages over Administration of Bacteria

As discussed in detail above, and in the attached Declaration under 37 C.F.R. 1.132 of Antoine Andremont, M.D., Ph.D., the specification clearly teaches that isolated enzymes, rather than bacteria producing the enzymes, are to be administered in the instantly claimed drug delivery compositions.

The administration of isolated enzymes offers specific advantages over the administration of bacteria. For example, the enzymes themselves present no risk of bacterial infection, in contrast to administering the bacteria itself to the colon. Further, there is no risk of transferring bacterial resistance from the bacteria which produce the enzymes to bacteria already present in the gut that do not produce such enzymes.

The isolated enzymes also suffer from disadvantages over the use of the bacteria themselves. As isolated peptides/proteins, they are more susceptible to degradation when administered in the oral route than the bacteria themselves.

Thus, it would not even be obvious from the teachings of Olshenitski to deliver the isolated enzymes.

Rejections under 35 U.S.C. 103 (a)

Claims 12-18, 28-36, 45-55, and 59-65 were rejected under 35 U.S.C. 103 (a) as obvious over Sriamoransak, Munjeri, Noguchi, and Ounissi.

Sriamoransak and Munjeri

Sriamoransak and Munjeri purportedly teach the incorporation of certain active agents into pectinate beads.

Noguchi and Ounissi

Noguchi and Ounissi were cited as purportedly teaching proteins, including isolates of the enzymes erythromycin esterase and macrolide 2'-phosphotransferase I (Mph(A), which are capable of inactivating antibiotics.

Purported Basis for the Rejection

The purported basis for the rejection is that the claims are a mere combination of old elements, by enclosing a specific active agent into a known pectinate bead.

Analysis

The purported basis for the rejection appears to be that pectin beads were known as a drug delivery vehicle, and the active agent to be delivered (agents which inactivate antibiotics) were also known, so it would have been obvious to combine these elements. This is an insufficient basis for an obviousness rejection.

In the instant case, while the primary references (Sriamoransak and Munjeri) do teach that pectin beads can be used to deliver certain active agents (bovine serum albumin in one case, and an antimalarial compound in the other), they do not teach using pectin beads to deliver enzymes, let alone enzymes which would inactivate antibiotics. The primary references do not teach any reason why one would administer enzymes which inactivate antibiotics to the colon.

Secondary reference Noguchi looked at how transcription of the mph(A) gene for macrolide-2'-phosphotransferase I in E. coli is regulated. Noguchi's conclusion was that the production of the Mrx and MphR(A) proteins in those E. coli that had an mphA operon should be enhanced in the presence of erythromycin (see the last paragraph on page 5057). It is unclear what, if anything, this has to do with the colonic delivery of an enzyme that inactivates erythromycin. If anything, Noguchi seems to suggest that such colonic delivery would not be necessary, because the presence of erythromycin would enhance the natural production of this enzyme in those bacterial strains with an mphA operon, and would inherently inactivate the antibiotic. Noguchi certainly did not disclose or suggest pharmaceutically beneficial effects of the macrolide-2'-phosphotransferase I enzyme produced by the bacteria, only how its production is regulated.

Secondary reference Ounissi discloses having cloned and sequenced the ereA gene in certain E. coli strains, which gene is responsible for producing an erythromycin esterase. Similarly, Ounissi does not disclose or suggest any pharmaceutically beneficial effects of the erythromycin esterase enzyme produced by the bacteria, only the sequence for the gene responsible for its production.

Importantly, as highlighted in the attached Declaration under 37 C.F.R. of Antoine Andremont, M.D., Ph.D., neither of the secondary references teaches any reason to isolate the enzymes, but rather, merely disclose the manner in which the bacteria produce the enzymes. The logical reason behind determining how the bacteria produce the enzymes is to develop agents which either stop the bacteria from producing these enzymes (i.e., so the antibacterial agents will not be inactivated), or to produce antibacterial agents which are immune to these enzymes ((i.e.,

so the antibacterial agents will not be inactivated (again, so the antibacterial agents will not be inactivated). No reference provides any motivation to isolate the enzymes from the bacteria, to use them for any legitimate pharmaceutical purpose, or to deliver them specifically to the colon.

Thus, the rejection is based solely on the fact that a) certain embodiments of the drug delivery vehicle used in the claims are known, and b) enzymes which are to be delivered in the drug delivery vehicle are known. The rejection lacks at least one critical feature – no combination of references provides any teaching, suggestion, or motivation to administer these active agents to the colon, for any purpose, let alone the articulated purpose in the specification.

While the pending claims are composition claims, rather than method claims, the reasons for incorporating an agent into a composition are absolutely relevant when one considers whether it would be obvious to combine references to arrive at the claimed compositions.

Accordingly, the rejection should be withdrawn, as there is absolutely no articulated basis in the references, or in the Office Action itself, to place an enzyme capable of inactivating an antibiotic in a formulation designed for colonic delivery. Indeed, the references do not even focus on isolating the enzymes, just on how they are produced. As discussed in detail above, there is no motivation to administer whole bacteria, and the secondary references cited in the obviousness rejection do not even teach isolating bacterial enzymes for incorporation into any drug delivery vehicle, much less the vehicle in the claims as pending.

To the contrary, research to identify enzymes capable of inactivating antibiotics has been conducted primarily to identify ways to deliver antibiotics that are resistant to these enzymes, or to identify agents that inactivate such enzymes (i.e., clavulanic acid and its salts). Absent impermissible hindsight, there would be no reason to place the enzymes disclosed in the

secondary references into the drug delivery vehicles in the primary references. The references provide no motivation to purposefully administer the enzymes to the colon, as required by the claims, to minimize the concentration of antibiotics in the colon.

To refute the arguments earlier presented, the Examiner points to the fact that the enzymes are indigenous to the colon, so it would be obvious to administer the isolated enzymes. This rationale cannot be sufficient to maintain an obviousness rejection.

First and foremost, the enzymes are produced only in certain strains of bacteria, so are not found in all patients. Indeed, the main purpose of the claimed invention is to prevent such strains from becoming prevalent as antimicrobial usage increases.

Secondly, respectfully, fecal matter is also indigenous to the colon, but there is no motivation to orally administer fecal matter in the hopes that bacteria present in the fecal matter might release enzymes which would inactivate antibacterial compounds in the colon.

For at least these reasons, the rejection should be withdrawn.

Conclusion

It is believed that the claims are currently in condition for allowance. The Examiner is encouraged to contact Applicants' undersigned representative if he has any questions regarding the above.

Respectfully submitted,

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Enclosures:
Declaration of Antoine Andremont [12 pgs.]